The logic, methodological and practical flaws of the Harm-Benefit-Analysis (HBA) in Directive 2010/63/EU

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Abstract: Directive 2010/63/EU regulates the use of animals for scientific purposes in EU member states and mandates that every project proposal involving procedures on living non-human vertebrates and cephalopods has to be approved in a review process that includes a Harm-Benefit-Analysis, to assess "whether the harm to the animals in terms of suffering, pain and distress is justified by the expected outcome taking into account ethical consideration and may ultimately benefit human beings, animals or the environment (EU Directive 2010/63, Art 38d). The aim of this paper is 1) to summarize recent criticism on the epistemic and practical limitations of the prospective benefit assessment in the HBA in its current form and on the focus on tangible societal benefits in project evaluation and 2) as a proof of principle, demonstrate the argumentation of these papers on 2 concrete examples, namely the insulin inhalator Exubera and the cancer drug Ipilimumab. First, we show that the HBA suffers from a logical and methodological flaw. The outcome of an experiment is per definition uncertain. If it wasn't, the experiment would not generate new knowledge and would therefore be illegal. Moreover, as long as animals are used as models for humans there will always be uncertainty regarding the translatability of knowledge from model to target species. Second, we show that practical flaws further complicate prospective benefit assessment. There are non-scientific factors, such as market potential, lobbying, patient compliance, etc., that are impossible to predict and yet, are important parameters in prospective benefit assessment. Together, these uncertainties make a prospective benefit assessment implausible. Also, the requirement to demonstrate societal benefits might incentivize researchers to overstate the tangible benefits of their research in project proposals, thereby making prospective benefit assessment in project evaluation more difficult for committees. Overstating potential societal benefits that are eventually not realized might also be detrimental to the credibility of science. In light of these flaws we think it necessary to develop an alternative model for project evaluation that focuses on potential knowledge gains as outcome of a project rather than prospective assessment of potential societal benefits.

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Abstract

Directive 2010/63/EU regulates the use of animals for scientific purposes in EU member states and mandates that every project proposal involving procedures on living non-human vertebrates and cephalopods has to be approved in a review process that includes a Harm-Benefit-Analysis, to assess "whether the harm to the animals in terms of suffering, pain and distress is justified by the expected outcome taking into account ethical consideration and may ultimately benefit human beings, animals or the environment (EU Directive 2010/63, Art 38d).

The aim of this paper is 1) to summarize recent criticism on the epistemic and practical limitations of the prospective benefit assessment in the HBA in its current form and on the focus on tangible societal benefits in project evaluation and 2) as a proof of principle, demonstrate the argumentation of these papers on 2 concrete examples, namely the insulin inhalator *Exubera* and the cancer drug *Ipilimumab*.

First, we show that the HBA suffers from a logical and methodological flaw. The outcome of an experiment is per definition uncertain. If it wasn't, the experiment would not generate new knowledge and would therefore be illegal. Moreover, as long as animals are used as models for humans there will always be uncertainty regarding the translatability of knowledge from model to target species. Second, we show that practical flaws further complicate prospective benefit assessment. There are non-scientific factors, such as market

potential, lobbying, patient compliance, etc., that are impossible to predict and yet, are important parameters in prospective benefit assessment. Together, these uncertainties make a prospective benefit assessment implausible.
Also, the requirement to demonstrate societal benefits might incentivize researchers to overstate the tangible benefits of their research in project proposals, thereby making prospective benefit assessment in project evaluation more difficult for committees. Overstating potential societal benefits that are eventually not realized might also be detrimental to the credibility of science. In light of these flaws we think it necessary to develop an alternative model for project evaluation that focuses on potential knowledge gains as outcome of a project rather than prospective assessment of potential societal benefits.

Key Words: Harm-Benefit-Analysis, animal research ethics, Project evaluation, Credibility of research, Benefit concept

Introduction

Directive 2010/63/EU mandates that every research proposal entailing experiments on living non-human vertebrates and cephalopods is evaluated in a „harm-benefit-analyis“ (HBA) to assess “whether the harm to the animals in terms of suffering, pain and distress is justified by the expected outcome taking into account ethical consideration and may ultimately benefit human beings, animals or the environment (EU Directive 2010/63, Art 38d). From this it follows, that societal benefit (in terms of practical benefits for human, animals or the environment) and animal harm are competing interests that ought to be and can be weighed against each other. The HBA thus functions as legal as well as moral evaluator of research projects. Due to moral concerns regarding animal suffering, we agree that animal research should be regulated very strictly. However, we claim that the HBA as the current evaluation method to decide on what is scientifically and morally justified research has conceptual and practical flaws that make it unsuitable for its purpose (Eggel and Grimm, 2018a, under revision). These flaws are connected to the nature of the relation between “outcome” and “benefit” (Eggel and Grimm, 2018a, under revision) and to the focus on societal benefits within the HBA (Bateson P. 1986., Bout et al. 2014., Brönstad et al. 2016., Hirt et al 2015.,

Laber et al. 2016., Scharman and Teutsch. 1994., Stafleu et al. 1999., EWG for project evaluation. 2013). The outcome of an experiment (i.e. knowledge) has been attributed little justifying power in a HBA compared to societal benefits (Eggel/Grimm. 2018a, under revision). The potential of the knowledge to turn into societal benefit is considered to be a more valid benefit able to outweigh inflicted harm on animals. But exactly here lies the problem; prospective assessment of potential societal benefits of research projects in a HBA is, due to epistemic and practical flaws that are connected to the inherent uncertainties of the scientific process, vague speculation at best and thus, unsuitable for legal and moral project evaluation. In the following, we will 1) summarize the argumentation of recent publications that critizise the current harm-benefit-analysis in project evaluation due to logic, methodological and practical flaws (Grimm et al. 2017., Grimm and Eggel. 2017., Eggel and Grimm. 2018a, under revision., Eggel and Grimm 2018b, submitted) and 2), as a proof of principal, we demonstrate the argumentation of these papers on two concrete examples, namely the insulin inhalator *Exubera* (Heinemann et al. 2008) and the anti-cancer drug *Ipilimumab* (Williams et al., 2015).

It is important to note, that we do not question on a principle level whether animals ought to be used for research. Our argumentation starts from a "real world" assumption, where as a matter of fact animals are used in research under particular legal requirements. Also, our argumentation is based on the moral premise of the Directive, which is based in consequentialist moral theory. We will show, that based on that premise, the HBA in its current form fails to meet its goal (i.e. ethical evaluation of research proposals) due conceptual and practical flaws and should be replaced by a different model that replaces "harm-benefit-analysis" with a "harm-knowledge-analysis" (Eggel and Grimm. 2018b, submitted).

Epistemic flaws of the HBA in project evaluation

In hypothesis-driven research, or any research for that matter, the goal is to answer an unsolved question, i.e. to produce new knowledge. Thus, the outcome of research is per definition unknown; before performing an experiment, one does not know whether a hypothesis will be verified or falsified or whether unintended knowledge will be produced. If the outcome of an experiment was clear, there would be no knowledge gained and thus, there would be no reason to perform the experiment and it would ethically as well as legally

be wrong to do so. The implication of this for the HBA is not trivial. The HBA clearly favours societal benefits over knowledge (Eggel and Grimm, 2018a, under revision). Here, we argue that for prospective benefit assessment only verification and only in exceptional cases the falsification of a hypothesis will contribute to the potential generation of societal benefit. After all, drug discoveries for example, usually happen on the back of positive results and to a far lesser extent on negative results. However, as mentioned above, whether the hypothesis will be verified or falsified is unknown. This inherent uncertainty of hypothesis-driven research makes prospective evaluation of societal benefit implausible.

This logical flaw is exacerbated further by the methodological flaw that is associated with the uncertainty of translatability (Eggel and Grimm, 2018a, under revision). Animals are used as model organisms to study human diseases. A model organism in this context is per definition never the same as the target species, i.e. humans. The knowledge gained in animals thus can't always in its entirety be translated to human application. In general, one can say that the translatability increases with greater similarity. However, since there will always be differences between model and target species, there will also always be uncertainty regarding the translatability of the knowledge gained. Since prospective benefit assessment is dependent on translatability, it is strongly affected by the uncertainty of translatability.

Practical flaws

So far, we have elaborated on science-internal factors, e.g. uncertainty of outcome and uncertainty of translatability. Next to these logic and methodological flaws there are also extra-scientific, practical flaws that further complicate prospective assessment of societal benefits (Eggel and Grimm, 2018a, submitted). Whether societal benefit is realized does not only depend on knowledge gained in research. The knowledge gained in research can only ever be a necessary but never sufficient condition for the generation of societal benefits. This is due to the fact, that extra-scientific factors, such as market potential (Qureshi et al. 2011., Heinemann. 2008), patient compliance (Hunter et al. 1999), lobbyism (Miller et al. 2007., Ventola et al. 2011), a.o. play a crucial role for the human application of knowledge gained research. This is illustrated by the fact that drugs that are approved for application never make it to the market or are discontinued (importantly, we are not talking about drugs that are withdrawn for safety or efficacy reasons but rather because they showed limited

market potential or failed due to low patient compliance) Qureshi et al. 2011., Heinemann. 2008. Orphan diseases (Aronson et al. 2006) represent an example, where a genuine medical need does not translate into sufficient market potential. Furthermore, the nonsteroidal anti-inflammatory drug *Duract* (Hunter at al. 1999), had to be withdrawn from the market because it caused kidney failure because patients took it longer than indicated – the drug was effective and safe, however it failed due to patient compliance. Also, approved drugs first need to be integrated into treatment regimens of doctors and hospitals. This might sound trivial, however, these decisions are not only based on medical merits of drugs, e.g. they are also influenced by lobbying (Miller et al. 2007., Ventola et al. 2011). These are only but a few "proof of principle" examples, that illustrate that there are non-controllable factors outside the scope of research, that further complicate a prospective benefit assessment in project evaluation.

The American association for laboratory animal science („Aalas") and the European federation of laboratory animal science association („Felasa") working group on the harm-benefit-analysis states that "Since HBA drives ethical reflection and discussion on current practices, it is important for building public support…" (Brönstad et al., 2016). While we agree, that the Directive and the HBA were formulated with good intentions we think that they might actually not build but rather erode public support in the long term. In our opinion this is due the fact that scienctists are incentivized to speculate on the potential societal benefits of their research in project proposals and thus might be incentivized to promise too much. This might be a problem for two reasons. First, overstating societal benefits makes project evaluation more difficult for competent national authorities. Furthermore, „non-technical project summaries" are a mandatory requirment in writing a project proposal and they are open to the public. Thus, repeated failure of science to meet self-proclaimed goals (i.e. societal benefits) might erode the trustworthiness of science in the long term.

The cancer drug *Ipilimumab* and the Insulin Inhalator *Exubera* as „proof of principle" examples

In the following we will use *Exubera* and *Ipilimumab* as two „proof of principle" examples to demonstrate the logic, methodological and practical flaws of the HBA in current project evaluation. It was shown that the discovery and market approval of the cancer drug

Ipilimumab was mainly contingent on 433 basic and applied research publications over 46 years (Williams et al. 2015). However, the HBA with its focus on prospective assessment of potential societal benefits implies a rather direct causality between a research project and the generation of a new therapeutic drug. When looking at the above example, the nature of this causality becomes rather indirect, i.e. not a single research project generates societal benefit, but rather literally hundreds of projects over many decades. If one acknowledges the logic and methodological limitations of prospective assessment, i.e. in each of these studies the outcome of the research and the translatability of the results are uncertain, then it becomes salient that a prospective benefit assessment of single research projects in animal research that goes beyond the assessment of knowledge is not plausible.

Furthermore, the financial failure of the Insulin inhalator Exubera is a good example to demonstrate the practical limitations of prospective benefit assessment. Exubera, although effective and safe, never really generated a societal benefit, since it was taken off the market already after one year of its approval due to low sales numbers. The main reason for the low sales numbers were not limited efficacy or safety issues, but is rather comical and simple – the inhalator was just too big (Heinemann, 2018). The device was, from a scientific point of view smartly designed to optimize insulin application into the deep lung, but did not accomodate for the patient's wish for discretion. If you used this inhalator in a public space you would draw a lot of attention. Also, inhalation of a large dose of insulin was time-consuming and the teaching efforts necessary to use the inhalator were underestimated by the manufacturer (Heinemann, 2018). This example illustrates that even in cases, where one assumes that all the speculations regarding potential benefits gained from a research project will hold true, i.e. generation of Insulin therapeutic; it is still uncertain what actual societal benefit might arise from it, due to uncontrollable, extra-scientific factors.

Another striking example is the discovery of CRISPR-Cas9. This obscure microbial system, discovered 20 years ago in a salt marsh at the Costa Blanca in Spain is revoluzioning agriculture, research and medicine (Lander, 2016). Interestingly, the early research on CRISPR was not a quest to edit DNA, nor a study of human diseases. It was a hypothesis-free study of odd DNA sequences with unknown biological function without any foreseeable benefit to society. This is not to say that „hypothesis-driven" research is not very important but rather an acknowledgement that big scientific breakthroughs are often serendipitous

and completely unpredictable. Since the early work on CRISPR was done in prokaryotes, these research proposals did not have to pass a HBA. However, it is quite obvious that these proposals would have had a hard time demonstrating potential societal benefits.

Conclusion

Summarizing arguments from recent publications (Grimm et al. 2017., Grimm and Eggel. 2017., Eggel and Grimm. 2018a, under revision., Eggel and Grimm 2018b, submitted) we have argued that the HBA suffers from a logic flaw connected to the uncertainty of the outcome of an experiment and a methodological flaw connected to the uncertainty associated with the translatability of knoweldge gained in model organisms. Furthermore, we have shown that a practical flaw regarding non-controllable, extra-scientific factors further exacerbates the problem of prospective benefit assessment.

Also, we believe that scientists might be incentivized to overstate the potential societal benefits of their research, which could further complicate project evaluation for competent authorities from a practical perspective. Next, we have argued that the focus on societal benefits might not only have implications for the HBA, but also might have consequences regarding the credibility of research in the long term (Grimm and Eggel, 2017., Grimm et al. 2017).

We have argued that prospectively assessing societal benefits is vague speculation at best and is thus not well-suited for legal and ethical evaluation of project proposals. We believe that knowledge can be more accurately assessed prospectively compared to societal benefits. Thus, we propose to replace the current harm-benefit-analysis (HBA) with a harm-knowledge-analysis (HKA) (Eggel and Grimm, 2018b, submitted) which evaluates the expected knowledge contribution of a project to a research field rather than societal benefits. To maximize epistemic benefit, project evaluation would focus on scientific factors, e.g. scientific merit, strength of hypothesis, experimental setup, a.o.. The parameters described are not new to scientists. These are parameters that are already used in peer-review and thus one can expect researchers to have little trouble complying with them. By focusing on knowledge, rather than benefit, our proposal would also overcome the uncertainty regarding translatability and the problem associated with uncontrollable extra-scientific factors. Also, scientists would no longer be incentivized to promise too much and

thus, the HKA might be beneficial for the credibility of science. Importantly, our model separates scientific from ethical assessment in project evaluation. We believe that the decision on the ethical acceptability of animal research should not be decided by competent authorities but should be decided in the political arena.

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